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APPLICATION NO.	FILING D	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/484,895	Applicant(s) HARRINGTON ET AL
	Examiner Quang Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-116* is/are pending in the application.

4a) Of the above claim(s) *110-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-109 and 113-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,5,8,9*
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Applicants' response to Restriction Requirement in Paper No. 6 is acknowledged. However, pursuant to telephonic conversations with Ms. Anne Brown, Examiner retracted the Restriction Requirement dated 03/29/01 in Paper No. 5, and issued the following new Restriction Requirement. Unpublished PCT International search report has been considered but its listing has been crossed out on PTO-1449.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 58-109 and 113-116, drawn to a vector, a host cell, a library of cells comprising the same and methods for activating an endogenous gene or identifying a gene in a cell; for isolating cells in which a single exon gene has been activated; for isolating exon I of a gene; for expressing a transcript containing exon 1 of a gene and for producing a gene product encoded by an endogenous cellular genomic gene. classified in class 435, subclasses 320.1. 455. 69.1.

II. Claims 110-112, drawn to a protein produced by the methods of the instant claimed invention, classified in class 530, subclass 350+.

Should Group I is elected, a further election of species is required.

Claims 58, 65, 67, 70, 71, 73 and 76 are generic to a plurality of disclosed patentably distinct species comprising:

A specifically named amplifiable marker as listed in the Markush group of claim 76.

Claims 58, 65, 67, 70, 71, 74 and 77 are generic to a plurality of disclosed patentably distinct species comprising:

A specifically named viral origin of replication as listed in the Markush group of claim 77.

Claims 102, 105 and 108 are generic to a plurality of disclosed patentably distinct species comprising:

A specifically named cloning vector as listed in the Markush group of claim 108.

Claims 70 and 113 are generic to a plurality of disclosed patentably distinct species comprising:

A specifically named positive selective marker as listed in the Markush group of claim 113.

Claims 70 and 114 are generic to a plurality of disclosed patentably distinct species comprising:

A specifically named negative selective marker as listed in the Markush group of claim 114.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over

the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are drawn to distinct products capable of separate uses. The vector of Group I can be used to as a probe in hybridization assays whereas the protein of Group II can be used to produce antibodies. Additionally, the vector of Group I is made up of nucleotides whereas the protein of Group II is composed of amino acid residues.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, and separate search requirements, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Anne Brown on July 12, 2001 a provisional election was made without traverse to prosecute the invention of Group I, claims 58-109 and 113-116; with the following elected species: Dihydrofolate reductase for claim 76; Epstein Barr virus ori P for claim 77; BAC for claim 108; Neomycin gene for claim 113 and Thymidine kinase gene for claim 114. Affirmation of this election must be made by applicant in replying to this Office action. Claims 110-112 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-109 and 113-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for :

(i) A vector comprising: (a) a first promoter operably linked to an exon and an unpaired splice donor site located 3' downstream from said exon, and (b) a second promoter operably linked to a selectable marker encoding DNA sequence lacking a polyadenylation signal, wherein the first promoter and the second promoter are present in said vector in the same direction;

(ii) A vector comprising a first promoter and a second promoter, said first promoter and second promoters being oriented in the same direction, wherein: (a) said first promoter, but not said second promoter is operably linked to an exon and an unpaired splice donor site located 3' downstream from said exon, and (b) said vector comprises no polyadenylation signals downstream of either said first promoter or said second promoter;

(iii) A vector comprising: (a) a first promoter operably linked to a first selectable marker encoding DNA sequence containing an unpaired splice donor site, and (b) a second promoter operably linked to a second selectable marker encoding DNA sequence, wherein neither said first selectable marker encoding DNA sequence nor said second selectable marker encoding DNA sequence contains a polyadenylation

signal, and wherein the first promoter and the second promoter in said vector being oriented in the same direction;

(iv) A vector construct comprising: (a) a first promoter operably linked to a positive selectable marker encoding DNA sequence, (b) a second promoter operably linked to a negative selectable marker encoding DNA sequence, and (c) an unpaired splice donor site, wherein said unpaired splice donor site is located 5' upstream of or within said negative selectable marker encoding DNA sequence and wherein said unpaired splice donor site is located 3' downstream of said positive selectable marker encoding DNA sequence, such that when said vector construct is integrated into a genome of a eukaryotic host cell and an endogenous gene in said genome is transcriptionally activated, the positive selectable marker is expressed in active form and the negative selectable marker is either not expressed or expressed in an inactive form;

(v) an isolated host cell, a library of cells comprising any one of the above vectors and *in vitro* methods for activation of an endogenous gene in a cell; for identifying a gene wherein the identification in step (f) is accomplished by sequencing the cDNA and comparing the nucleotide sequence of the cDNA to the nucleotide sequence of the vector; for isolating cells in which a single exon gene that has been activated using the vector of claim 97, wherein the unpaired splice donor site is positioned upstream of the first selectable marker encoding DNA sequence; for isolating exon I of a gene; for expressing a transcript containing exon I of a gene; for producing a gene product encoded by an endogenous cellular genomic gene and for producing a

protein as claimed; does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 58-78, 97 and 113-116 are drawn to a vector having the limitations recited in the claims. Claims 79-92 are directed to a host cell and a library of cells comprising any one of the vectors of the present invention. Claims 93-96 are drawn to methods for activation of an endogenous gene and for identifying a gene in a cell using the vector of any one of claims 58, 65, 67, 70 or 71. Claims 98-99 are drawn to a method for isolating cells in which a single exon gene has been activated using the vector of claim 97. Claims 100-109 are directed to methods for isolating exon I of a gene, for expressing a transcript containing exon I of a gene, for producing a gene product encoded by an endogenous cellular genomic gene and for producing a protein using the vector of any one of claims 58, 59, 61, 65 or 67 or the same vector-genomic DNA complex.

The specification is not enabled for the instant broadly claimed invention for the reasons discussed below.

With respect to claims 58-64, the essential feature of the claimed vector is that a first promoter operably linked to an exon and an unpaired splice donor site located 3' downstream from said exon, in order for the vector to be used as contemplated by Applicants, such as for activating an endogenous gene or for identifying a gene in a cell and others via splicing with an endogenous splice acceptor. However, the claims merely recite the components present in the vector, and in broad claims (claims 58, 62-64) it is not even clear if there is any structural relationship between the first promoter and the second promoter as recited. Since the instant specification fails to provide sufficient guidance for a skilled artisan on how **to use** the vector regardless where the recited components in the vector are located, it would have required undue experimentation for a skilled artisan to practice the full scope of the vector as claimed. On the basis of the instant specification, it is unclear to Examiner what is the relevance of the second promoter operatively linked to a selectable marker encoding DNA sequence lacking a polyadenylation signal in the claimed vector? Regardless whether this second promoter is located downstream or upstream of the first promoter, how would the selectable marker be used and expressed in the instant invention? Although a fusion mRNA comprising the sequence encoding for the selectable marker along with the sequence of an endogenous gene with a polyadenylation signal could be made, but it is unclear and uncertain from the present specification that the selectable marker would be expressed and it would display its intrinsic selectable property, especially one

has to take into considerations of the folding and the stability of such a large fusion mRNA message (depending on where the vector is integrated into the 5' upstream of an endogenous gene).

Regarding to claims 65-66, the claimed vector merely requires the first promoter is operably linked to an unpaired splice donor site, without any recitation whether there is an exon or a selectable marker encoding DNA sequence operably linked to the first promoter or to the second promoter. The present specification does not provide any teaching regarding the use of any vector having simply promoters without operably linked to any exon and an unpaired splice donor site. As such, it would have required undue experimentation for a skilled artisan to use the vector as claimed. It should be noted that any critical element required for the practice of the instant invention has to be recited in the claim.

With respect to claims 67-69 and 97, as recited the broad claims do not indicate if there is a structural relationship between the first promoter and the second promoter or that both components in (a) and (b) are required for the practice of the present invention. The instant specification fails to provide sufficient guidance for one skilled in the art on the use of either components of the vector separately. As such, it would have required undue experimentation for a skilled artisan to make and use the full scope of the vector as claimed. Furthermore, with respect to claim 97 as the claim being interpreted broadly, the specification fails to teach how the positioning of the unpaired splice donor site upstream of the first selectable marker encoding DNA sequence would result in the expression of the selectable marker in an active form? Or

how the positioning of the unpaired splice donor site within the first selectable marker encoding DNA sequence would result in the first selectable marker not being expressed at all? As written, the scope of the instant claim encompasses these embodiments and in the absence of guidance provided by the present specification, again it would have require undue experimentation for a skilled artisan to use the full scope of the vector as claimed.

Regarding to claims 70-71 and 113-116, the claims encompass any and all possible structural orientations for the combination of a first promoter, a second promoter and an unpaired splice donor site in the vector to attain the functional limitation recited in claim 70. Apart from the scope given to this vector, it is unclear to Examiner which other possible combinations of the recited components can be made in the vector such that the functional limitation is met. As an example, with respect to the vector of claim 115, wherein the negative selectable marker encoding DNA sequence is located upstream of the positive selectable marker encoding DNA sequence, how would a negative selectable marker is either not expressed or is expressed in an active form (the limitation requires the positioning of an unpaired splice donor site 5' upstream of or within the negative selectable marker encoding DNA sequence, respectively) and at the same time the positive selectable marker is expressed in an active form in such a structural orientation? The instant specification, which is a long compilation of four related applications, fails to provide sufficient and clear teachings on how the embodiment of claim 115 is enabled. As such, with the lack of sufficient guidance

provided by the present application, it would have required undue experimentation for a skilled artisan to use the full scope of the vector as claimed.

The instant claims encompass both *in vitro* and *in vivo* host cells comprising the vectors of the present invention as well as both *in vitro* and *in vivo* methods of uses utilizing the same vectors. However, apart from the disclosure for the construction of various vectors for non-targeted activation of endogenous genes in a cell, and exemplification of using such vectors in cultured cells, the instant specification fails to provide sufficient guidance for a skilled in the art on the specific parameters or conditions of using the vectors of the instant invention *in vivo*. Relevant information, such as specific dosages of a particular vector or transformed or transfected cells used, the route of delivery utilized, the specific *in vivo* conditions deployed for the contemplated non-homologous integration of the vectors into a cellular genome, are not taught by the present specification. When read in light of the specification, certain embodiments of the instant claims encompass the production of any and all activated endogenous genes *in vivo* for the purpose of producing the activated gene products as well as for therapeutic purposes (see instant specification, page 51, lines 51-29; page 54, lines 26-27). With the lack of sufficient teachings provided by the specification and since the *in vivo* aspect of the methods as claimed is not considered to be routine in the prior art at the effective filing date of the present application, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention. Moreover, the physiological art is recognized as unpredictable (MPEP

2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that. once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With respect to the contemplated therapeutic use for the instant claims, it should be noted that the nature of this embodiment would fall within the art of gene therapy which at about the effective filing date of the present application was still considered to be immature and unpredictable. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed to make gene therapy a reality. Dang et al. also pointed out several factors limiting an effective human gene therapy, including suboptimal vectors, the lack of long term and stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues (last paragraph, col. 2, page 474). There is no evidence of record in the present specification indicating that any therapeutic effect has been achieved by the host cells or the claimed methods, nor does the instant specification provide guidance for a skilled artisan on how to over come the aforementioned factors known to limit the effective of gene therapy. The lack of a stable and long term transgene expression *in vivo* is supported by numerous teachings in the art. For examples, Palmer et al. (Proc. Natl. Acad. Sci. 88:1330-1334, 1991) demonstrated that the *in vivo* expression of human factor IX by transplanted syngeneic

recombinant fibroblasts was transient and vanished 1-5 weeks post-transplantation. Riddell et al. (Nature Med. 2:216-223, 1996) reported that five out of six patients seropositive for human immunodeficiency virus developed cytotoxic T-lymphocytes responses specific to a novel protein and eliminated infused autologous CD8+ HIV-specific cytotoxic T cells transduced with a fusion suicide gene (See abstract). Additionally, the instant claims encompass any and all routes of delivering the vectors of the present invention *in vivo*. However, vector targeting *in vivo* to desired cells or organs for achieving therapeutic effects continues to be unpredictable and inefficient. This is supported by numerous teachings in the art. As an example, Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They also indicated clearly that resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that an efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type." (page 240, sentence bridging columns 2 and 3). The instant specification fails to teach that any of the vectors of the present application could be delivered to desired target cells or tissues by any and all modes of administration such that it could activate any and all endogenous cellular genes to yield contemplated therapeutic effects. As such, it would

have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Regarding to claims 94 and 95, the broad claim encompasses any and all steps without reciting them for identifying a gene in one of the isolated cDNA molecules. However, apart from direct sequencing of the gene, how else would one be able to identify such gene? Hybridization does not allow one to obtain the identity of a gene. This is because depending on the G+ C content and hybridization conditions, any polynucleotide having complementary 10-20 nucleotides can form a stable complementary duplex approaches that of any much longer complex, and therefore the identity of the polynucleotide is still not clearly determined or established. In the absence of sufficient guidance provided by the present specification in this regard, it would have required undue experimentation for a skilled artisan to make and use the full scope of the method as claimed.

With respect to claims 98 and 99, as written the claims encompass the use of the vector of claim 97 in which the unpaired splice donor site is positioned upstream of or within the first selectable marker encoding DNA sequence. With the presence of an unpaired splice donor site within the first selectable marker encoding DNA sequence of vector 97, and thereby disrupting the expression of the first selectable marker. Then how can cells whose genomes comprised of the integration of such a vector be selected for the expression of both first and second selectable markers as claimed in step (c). In the absence of any guidance provided by the instant specification regarding to this

matter, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological and gene therapy arts, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-109 and 113-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 58, 67, 70 and their dependent claims, the phrase "selectable marker" renders the claims unclear and therefore indefinite. This is because a marker is usually referred to a protein in the art, then how does a promoter is operatively linked to a protein in a vector? Do applicants mean a selectable marker encoding DNA sequence? Clarification is requested since the metes and bounds of the claims can not be clearly determined. Similarly, for the same reasons the phrase "amplifiable markers" in claims 73 and 76 renders the claims unclear because the markers are referred to protein molecules such as dihydrofolate reductase, adenosine deaminase, aspartate

transcarbamylase as recited in claim 76, and it is unclear how a protein molecule is comprised within a vector.

In claims 58 and 62-64, it is unclear what is the relationship between the component (a) and the component (b) of the claimed vector. Are they structurally linked within the same vector or not? If they are please recite in the claims as such. The metes and bounds of the claims can not be clearly determined. Clarification is requested.

In claims 65 and 66, it is unclear what is encompassed by the phrase "said first promoter, but not said second promoter, is operably linked to an unpaired splice donor site". Normally, a promoter is operably linked to an exon not to unpaired splice donor site. Is there an exon operatively linked to the first promoter or not? The metes and bounds of the claims can not be clearly determined. Clarification is requested.

In claims 67-69, it is unclear what is the relationship between the component recited in (a) and the component recited in (b). Are they structurally linked within the same vector? If so, please recite the claims as such. Clarification is requested.

In claim 70 and its dependent claims, it is unclear what is encompassed by the phrase "said splice donor site are oriented in said vector construct in an orientation that, when said vector construct is integrated into the genome of a eukaryotic host cell in such a way that an endogenous gene in said genome is transcriptionally activated, then said positive selectable marker is expressed in active form and said negative selectable marker is either not expressed or is expressed in inactive form", and therefore it renders the claims indefinite. Although the functional limitation is disclosed, it is unclear about

the structural orientation of the splice donor site with respect to the first promoter and to the second promoter in the claimed vector in order to attain the desired functional limitation. Since the structural orientation of the splice donor site with respect to other components of the vector is critical for the vector's property, it is essential that the structural orientation must be particularly pointed out in the claimed vector. Along the same line, with respect to claim 71, it is unclear what is the structural orientation of a third promoter operably linked to a second unpaired splice donor site with respect to other components of the vectors in order to attain the functional limitation recited in the claim. Clarification is requested.

In claims 98 and 99, the phrase "in which said first and second selectable markers are expressed in their active forms" in step (c) is unclear and it renders the claims indefinite. This is because using the vector of claim 97 as it is integrated into the genome of a eukaryotic host cell, the first selectable marker is expressed in inactive form or is not expressed at all as recited in claim 97. Then, using the same vector how can both first and second selectable markers are expressed in their active forms? Particularly, the unpaired splice donor site is positioned within the first selectable marker, and thereby disrupting the marker. Clarification is requested.

In claim 99, it is unclear what is the relationship between the steps (d)-(f) and the isolation of cells in which a single exon gene has been activated as recited in the preamble of claim 98 from which claim 99 is dependent upon. The method for isolating cells as recited in claim 98 is already completed with step (c). Should Applicants intend

to claim a method for isolating a single exon gene in isolated cells in which a single exon gene has been activated, it should be claimed independently.

In claim 100, it is unclear what is encompassed by the phrase "using said vector exon-tagged cDNA molecules to recover the activated endogenous gene containing exon I" in step (g) because it is unclear which steps are involved in the recovery of the activated endogenous gene using said vector exon-tagged cDNA molecules. Clarification is requested.

In claim 102, it is unclear what is encompassed by the phrase "otherwise combining with". The metes and bounds of the claim can not be clearly determined since it is unclear which other means other than inserting the isolated genomic DNA into one of the recited vectors. Clarification is requested.

In claims 103 it is unclear what is relationship between the steps (e)-(g) and the production of a gene product encoded by an endogenous cellular genomic gene recited in the preamble of claim 102 from which claim 103 is dependent upon. The method for producing a gene product as claimed is already completed in step (d) of claim 102.

Claim 116 recites the limitation "The cell of claim 115" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 115 is drawn to a vector without any recitation of a cell. Clarification is requested.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER